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10/511,273	06/27/2005	Kostas Kosmatopoulos	260449US0XPCT	5023

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EXAMINER
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ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
10/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/511,273	KOSMATOPOULOS ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-9* is/are rejected.

7)☒ Claim(s) *4 and 5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5 and 7-9 are all the pending claims for this application.

2. Claims 1, 3-5, 8 and 9-13 have been amended and Claims 6 and 10-29 deleted by amendment in the Response of 7/23/07.

3. Claims 1-5 and 7-9 are all the pending claims under examination on the merits.

4. Applicants amendments to the claims have raised new grounds for objection and rejection.

Information Disclosure Statement

5. The non-patent literature references cited in the IDS of 7/23/07 have been considered and entered.

Withdrawal of Objections

Oath/Declaration

6. The objection to the oath/declaration for containing non-initialed and/or non-dated alterations is withdrawn in view of the alterations having been entered after the filing. Applicants comments on the bottom of p. 7 of the Response of 7/23/07 are acknowledged.

Specification

7. The objection to the Abstract of Disclosure is withdrawn in view of the revised Abstract filed with the Response of 7/23/07.

8. The objections to the specification for the following informalities is withdrawn:

a) The submission of the copy of the original p. 1 for the specification does not contain non-initialed and/or non-dated alterations.

b) The deletions of the hyperlinks throughout the specification obviates the objection under MPEP § 608.01.

c) The objection to the original specification for failing to include a "Brief Description of the Drawings" is withdrawn in view of the amendment to the specification on pp. 2-3 of the Response of 7/23/07.

Additionally, the objection to Figure 1 which describes a polypeptide sequence and for which no sequence identifier is provided with the original figure, is withdrawn in view of the amended legend for Figure 1 to include the SEQ ID NO:1.

Applicants' comments on the top of p. 8 of the Response of 7/23/07 are acknowledged.

Claims

9. The objection to Claim 9 for reciting a typographical error "selected from a group" is withdrawn in view of the amended claim to recite "the group".

Withdrawal of Rejections

Claims - 35 USC § 112, second paragraph

10. The rejection of Claims 1-5 and 7-9 for the recitation "EphA2" is withdrawn in view of the amendment of Claim 1 to recite "Eck tyrosine kinase receptor (EphA2) protein."

11. The rejection of Claims 1-5 and 7-9 in lacking antecedent basis for the limitation "the EphA2 antigen" in Claims 1 and 3 is withdrawn in view of the amendment to substitute the term "antigen" with "protein."

12. The rejection of Claims 1-5 and 7-9 for the recitation "the EphA2 antigen" is withdrawn in view of the amendment to substitute the term "antigen" with protein".

13. The rejection of Claims 4 and 5 in lacking antecedent basis for the limitation "said peptide" is withdrawn in view of the amendment to recite "said immunogenic peptide."

14. The rejection of Claims 3 and 4 as being indefinite as to what properties confer the immunogenicity of the peptide is withdrawn in view of the amendment to recite that the at least one amino acid substitution increases the binding affinity and/or stability of the peptide.

15. The rejection of claim 3 for reciting the relative term "increases" in the phrase "increases the binding affinity and/or stability" is withdrawn in view the amendment to recite that the substituted peptide is compared to an unsubstituted peptide.

16. The rejection of Claims 8 and 9 for the phrase "comprising at least one selected from" is withdrawn in view of the amended claims to recite "at least one peptide selected from."

17. The rejection of Claims 8 and 9 for the phrases "other immunogenic peptides" and "another immunogenic peptide", respectively, is withdrawn in view of the amendment of the claims to recite "derived from the EphA2 protein or one or more other antigens."

18. The rejection of Claim 9 for reciting "a copy" of a chimeric peptide is withdrawn in view of the amendment to recite that the chimeric polypeptide comprises at least one copy of the immunogenic peptide.

Applicants' comments regarding the § 112, second paragraph rejection of the claims on pp. 8-9 of the Response of 7/23/07 are acknowledged.

Claims - 35 USC § 112, first paragraph

Written Description

19. The rejection of Claims 8 and 9 under 35 U.S.C. 112, first paragraph for reciting new matter with respect to nucleic acids encoding "other immunogenic peptides" (Claim 8) and compositions comprising both the EphA2 immunogenic peptide and a chimeric polypeptide (Claim 9) is withdrawn.

The amendment of Claim 8 to replace the limitation for polynucleotides with the limitation for the immunogenic peptides derived from the EphA2 protein and other immunogenic peptides derived from one or more other antigens obviates the rejection.

The amendment of Claim 9 to recite that the composition comprises a chimeric polypeptide comprising at least one copy of an immunogenic peptide derived from EphA2, and at least one copy of another immunogenic peptide derived from EphA2 or other antigens obviates the rejection.

Applicants' comments on the bottom of p. 9 of the Response of 7/23/07 are acknowledged.

Enablement

20. The rejection of Claim 1-5 and 7-9 under 35 U.S.C. 112, first paragraph, in lacking enablement for the peptides producing an immunogenic response in just any cancer patient because tolerance to normally expressed EphA2 must be overcome, or

for multiepitope compositions comprising different immunogenic EphA2 peptides combined with immunogenic peptides from other tumor antigens, or polyepitopic constructs such as chimeric polypeptides comprising the EphA2 peptides in combination with other tumor peptides, or nucleotides encoding any one EphA2 peptide or in combination with other tumor antigen peptides is withdrawn.

Applicants' allegations on pp. 11-13 of the Response of 7/23/07, the claim amendments and the 1.132 Declaration of Dr. Kosmatopoulos (section 3) have been considered and are found persuasive.

On p. 11-12 of the Response and under section 3 of the Declaration, Applicants have clearly explained the method technique(s) used for selecting the immunogenic peptides of the claimed invention, namely, the 3 criteria required in the "reverse immunology" antigen discovery method. Once these criteria are met, then the resultant peptide would necessarily be an immunogenic peptide meeting all of the limitations of the claims. The copies of the references (Kawashima, Tahara, Lu and Vonderheide) using the "reverse immunology" strategy in selecting immunogenic peptide(s) from non-analogous tumor-associated antigens are appreciated and have been considered as relevant art in the teaching of the "reverse immunology" method at the time of application filing.

On p. 13 of the Response, Applicants allege that peptide vaccine therapy has advanced beyond the Ezzell reference cited in the Office Action of 2/22/07 to where studies have reached Phase II and III clinical trial status (citing Neumunaitis, Gilboa and O'Mahony), and where in Table 1 (from the Neumunaitis reference), the list of current

trials is recited. Notably, Applicants have not made the correlation between the "reverse immunology" method used to select the inventive claimed peptides and whether those peptides discussed in the Neumunaitis, Gilboa and O'Mahony references (or in Table 1) were selected on the same basis. Notwithstanding, Applicants' admission of record on the bottom of p. 13 of the Response of 7/23/07 that "the claimed immunogenic peptide can be predictably obtained by using reverse immunology described in the specification and that this method has been successfully used by scientists to obtain various immunogenic peptides that were used in *preclinical* [Examiner's emphasis] vaccination studies" supports the use of the method as being more sensitive to selecting more relevant immunogenic peptides for cancer therapy in preclinical testing.

Further, Applicants' admission of record (middle of p. 13 of the Response; using a "*single* peptide and inducing a monospecific response" in humans), is a strong implication that the compositions of Claim 8 (multiepitope composition) and Claim 9 (chimeric polypeptide) were not enabled at the time of application filing for use in human cancer treatment or least for use beyond preclinical vaccine studies.

Finally, the amendment of Claim 8 to delete the composition comprising "polynucleotides encoding other immunogenic peptides" overcomes this aspect of the rejection.

Claims - 35 USC § 103

21. The rejection of Claims 1, 2 and 7 under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (USPN 20070031882; with priority filing date 2/15/2002) in view Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06) is withdrawn.

Applicants' allegations on pp. 14-15 of the Response of 7/23/07, the 1.132 Declaration of Dr. Kosmatopoulos (sections 3-5) and the Kessler et al. reference have been considered and are found persuasive.

Applicants allege that Parker's disclosed BIMAS method for selecting T-epitope peptides is distinguishable from the method used for selecting the inventive peptide because Parker's method omits the biological processing step as an analysis/selection step. Parker does not teach that the peptide can be processed in the proteasome and then presented by the MHC. Inasmuch as Powell discloses B-cell immunogenic epitopes in EphA2, Applicants allege that no motivation existed to combine the references.

On p. 2, section 4 of the 1.132 Declaration, Parker is discussed within the same context for its omission of teaching biological processing much less determing if a high HLA affinity peptide is an epitope based on the Kessler reference.

It is noted that Applicants method also relied on the BIMAS for original peptide selection but included "reverse immune" technology.

22. The rejection of Claims 1, 2 and 7 under 35 U.S.C. 103(a) as being unpatentable over Lindberg et al (Mol. Cell Biol. 10(12):6316-6324 (1990); cited in the IDS of 10/21/2004) in view Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06) and Renkvist et al. (Cancer Immunol. Immunother. 50:3-15 (2001); cited in the 892 form of 10/13/06) is withdrawn.

Applicants' allegations on pp. 15-17 of the Response of 7/23/07, the 1.132 Declaration of Dr. Kosmatopoulos (sections 3-5) and the Kessler et al. reference have been considered and are found persuasive.

Applicants allege that Lindquist is silent regarding the immunogenicity of the EphA2 protein, Renkvist teaches immunogenic peptides but none of which are obtained by "reverse immune" method and is silent regarding EphA2, and the comments regarding Powell and Parker are incorporated.

On pp. 2-3, section 4 of the 1.132 Declaration, Lindquist, Parker and Renkvist are discussed within the same context for their omissions in teaching biological processing much less determing if a high HLA affinity peptide is an epitope based on the Kessler reference.

New Grounds for Objection

Claim Objections

23. Claim 9 is objected to for the following informality: the term "antigenes" appears to be a misspelling of "antigens."

New Grounds for Rejection

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

24. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 are indefinite for the recitation "other immunogenic peptide(s) derived from one or more other antigens" (Claim 8) and "another immunogenic peptide derived from...one or more other antigens" (Claim 9). The term "derived" is not one, which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. Since it is not clear how the immunogenic peptide is to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds. The term can encompass peptides with amino acid substitutions, insertions, or deletions, chemically derivatized molecules or even mimetics. In the absence of a single art recognized meaning for the phrase and lacking a definition in the specification, one of skill in the art could not determine the metes and bounds of the claims.

Further, because the specification does not define the class of molecules comprising "other antigens", it is less clear how just any immunogenic peptide from just any antigen can be derived.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

25. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph for reciting subject matter that is not supported by the original specification.

Claims 8 and 9 are interpreted as being drawn to compositions comprising a genus of immunogenic peptides, where Claim 8 recite "other immunogenic peptide(s) derived from one or more other antigens" and Claim 9 recites "another immunogenic peptide derived from...one or more other antigens". The claims encompass an undefined genus of derivatives for an undefined genus of "other antigens".

The specification does not provide support for the claimed compositions comprising the genus of immunogenic peptides because the specification does not describe the changes that can be made to the infinite genus of peptides corresponding to the infinite genus of "other antigens".

Claim Rejections- 35 U.S.C. §103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

26. Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schirle et al. (J. Immunol. Methods 257:1-16 (2001); cited in the PTO 892 form of 2/22/07) in view of Powell et al. (USPN 20070031882; with priority filing date 2/15/2002; cited on the PTO 892 form of 2/22/07) as evidenced by Tatsumi et al. (Can. Res. 63:4481-4489 (8/2003)) and Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06).

The interpretation of Claims 1-3 and 7 is of record.

It would have been prima facie obvious to have produced the immunogenic MHC I-restricted, T-epitope peptides from the EphA2 protein over Schirle in view of Powell and Parker.

Schirle discloses HLA-restricted, T-epitope peptides obtained from reverse immunology strategy where predicted HLA- binding peptides are tested in binding and stability assays followed by analysis of in vitro proteasome-mediated digestions of peptides encompassing candidate epitopes. Schirle discloses prediction algorithms for by 20s proteasomes, FRAGPREDICT and PAPROC and additional peptide digest data from the literature. Schirle teaches that the goal of combining proteasomal prediction algorithms with epitope prediction is already possible using combinations of FRAGPREDICT and PAPROC with SYFPEITHI and BIMAS and that more accurate prediction can be based can be based on fully quantified protein digestion data as well as immunoproteasomal digestion data (p. 7, section 2.2). Schirle describes the "reverse immunology" approach as the most successful strategy for the identification of T cell epitopes, and where the strategy can be used to identify peptides from viral or tumor-specific proteins (p. 2, Col. 1, ¶2-3). Schirle appreciates targeting viral- and tumor-associated antigens using the "reverse immunology' method but does not specifically teach EphA2 derived peptides or substituted forms thereof.

Powell discloses the ephrin kinase or EphA2 protein [0012, SEQ ID NO:2], and using immunogenic peptides for B-epitopes in treating HIV/AIDS [0009- 0010; 0183-0185; 0274]. Powell teaches the full length EphrinA2 protein comprising sequences corresponding to SEQ ID NOS: 4, 6, 7 and 8 (see attached sequence search alignment from the Office Action of 2/22/07). Powell does not disclose identifying or using T epitope peptides derived from the EphA2 protein, but appreciates EphA2-derived

immunogenic peptides. As evidenced by Tatsumi, HLA-restricted, T-epitope peptides were inherent to the EphA2 protein because Tatsumi isolated immunogenic peptides.

Parker teaches methods (BIMAS program) to identify peptides potentially capable of binding to HLA-A*0201 and selecting those with CTL-inducing properties. Parker discloses examples of epitopes ranging from antigenic proteins from viruses such as HTLV and HIV and endogenous peptides (Table VII) selected for HLA restriction and CTL-inducing properties for immunotherapy. Parker teaches that it is possible to select and/or generate by substitution immunogenic peptides from normal, endogenously expressed proteins using the BIMAS method that would otherwise be tolerized by T-cells.

One skilled in the art at the time the invention was made would have been motivated to have produced the instant claimed immunogenic peptide and been assured of reasonable success in doing so based on the combined discloses of Schirle, Powell, Tasumi and Parker because Schirle explicitly teaches the advantages of selecting T-epitope, HLA peptides using the reverse immunology strategy over other methods, Parker discloses dominant anchor residues important in the HLA molecule for selecting T-cell peptide epitopes using the BIMAS program which is also disclosed in Schirle, and Powell discloses using immunogenic Epha2 derived peptides and where Powell was in possession of the entire ephrin A2 protein the T-epitopes were inherent to the EphA2 protein as evidenced by Tatsumi. Parker also provide the motivation to substitute amino acid residues into peptides in order to overcome tolerance, especially for endogenously expressed proteins.

One skilled in the art would have been reasonably assured of success in producing the peptide T-epitopes from the EphA2 protein because the protein sequence for the EphA2 protein was already disclosed by Powell and T-epitopes were inherent to the EphA2 protein as evidenced by Tatsumi, and because Schirle and Parker provide further method support for identifying T-epitopes with the properties of being HLA-restricted and immunogenic for T cells using methods comprising the BIMAS protocol and peptides further being selected by the "reverse immunology" strategy of Schirle having already been successfully isolated.

For all of the foregoing reasons, the claims were prima facie obvious at the time the invention was made over Schirle, Powell as evidenced by Tatsumi and Parker.

Conclusion

27. No claims are allowed.

28. Claims 4 and 5 are objected as depending from a rejected base claim but are otherwise allowable.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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